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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,561	06/19/2006	James McSwiggen	02-728-L (400.166US)	3830
20306 7590 04/04/2007 MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP 300 S. WACKER DRIVE 32ND FLOOR CHICAGO, IL 60606			EXAMINER GIBBS, TERRA C	
			ART UNIT 1635	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE 3 MONTHS			MAIL DATE 04/04/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/562,561	MCSWIGGEN ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Terra C. Gibbs	1635	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10 March 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3,14-21,30 and 35 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,14-21,30 and 35 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 December 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>See Continuation Sheet</u>                                    | 6) <input type="checkbox"/> Other: _____                          |

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :August 7, 2006 and December 8, 2006.

### **DETAILED ACTION**

This Office Action is a response to Applicant's Amendment and Election filed March 10, 2007.

Claims 2, 4-13, 22-29 and 31-34 have been canceled. Claims 1, 3, 14-16, 18-21, 30, and 35 have been amended.

Claims 1, 3, 14-21, 30, and 35 are pending in the instant application.

Claims 1, 3, 14-21, 30, and 35 have been examined on the merits.

### ***Election/Restrictions***

The previous Restriction Requirement mailed February 13, 2007 is moot in view of Applicant's Amendment filed March 10, 2007 to cancel claim 33.

### ***Information Disclosure Statement***

Applicant's information disclosure statement filed December 8, 2006 is acknowledged. The submission is not fully compliant with the provisions of 37 CFR §1.97, which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It is noted that an English translation of European Document 1144623 B1 has not been provided. Therefore, European Document 1144623 has not been considered on the merits. Also, only the Abstracts of WO 01/42443, WO 01/70944, WO 02/55692, and WO 02/55693 have been considered since the remainder of the WO Documents has not been translated in

English. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith. However, European Document 1144623 B1 has been lined through, indicating that the reference has not been considered, and it has been indicated that only the Abstracts of WO 01/42443, WO 01/70944, WO 02/55692, and WO 02/55693 have been considered.

Applicant's information disclosure statement filed August 7, 2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

### ***Priority***

It is noted that the instant application is the national stage entry of PCT/US/04/20516, filed June 25, 2004.

It is also noted that the instant application claims priority to a laundry list of U.S. Provisional Applications and pending U.S. Patent Applications. The reference should be updated to reflect applications for patents that are pending or that have been abandoned.

Applicant is reminded that the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco*

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*Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

It is noted the instant claims have been amended and are currently drawn to a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein (APP) RNA comprising SEQ ID NO:1905. The Examiner would like to point out that Applicants contend that SEQ ID NO:1905 represents GenBank entry NM\_000484 as disclosed at page 153 of the instant specification (see Applicant's Remarks filed March 10, 2007 at page 6, second to last paragraph). At the outset, it is immediately noticed that the sequence of GenBank Accession Number NM\_000484 contains thymine residues, where SEQ ID NO:1905 of the instant application has substituted the thymine residues with uracil residues.

The instant application claims priority to a number of parent applications including Provisional Applications 60/358,580 and 60/363,124, filed February 20, 2002 and March 11, 2002, respectively. Now then, referring to Provisional Application 60/358,580, it is noted that the Examiner cannot find support for SEQ ID NO:1905 or GenBank Accession Number NM\_000484.

Next, referring to Provisional Application 60/363,124, it is noted that this application has support for GenBank Accession Number NM\_000484. Therefore, the instant application has been afforded priority to Provisional Application 60/363,124, which was filed on March 11, 2002.

In summary, Applicants claim priority to a number of parent applications, including Provisional Application 60/358,580, however, Provisional Application 60/358,580 does not appear to have support for a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein (APP) RNA comprising SEQ ID NO:1905 as instantly claimed. In this regard, the instant claims have been afforded priority to the filing date of the Provisional Application 60/363,124, which was filed on March 11, 2002.

If Applicants believe that they are entitled to an earlier priority date, the Examiner urges Applicant to specifically point where support can be found for SEQ ID NO:1905 or GenBank Accession Number NM\_000484 in any other applications Applicants claim priority to.

### ***Drawings***

The drawings filed on December 27, 2005 are acknowledged and have been accepted by the Examiner.

### ***Specification***

The amendment filed March 10, 2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: In the Amendment filed March 10, 2007, Applicants have submitted a new sequence listing in

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which SEQ ID NO:1905 has been added. Applicants contend that SEQ ID NO:1905 represents GenBank entry NM\_000484 as disclosed at page 153 in the instant specification (see Applicant's Remarks filed March 10, 2007 at page 6, second to last paragraph). At the outset, it is noted the sequence of GenBank entry NM\_000484 was submitted and made of record on the information disclosure statements filed August 7, 2006 and December 8, 2006. Comparing GenBank entry NM\_000484 with SEQ ID NO:1905 of the instant application, it is immediately noticed that the sequence of the Accession Number contains thymine residues, where SEQ ID NO:1905 has substituted the thymine residues with uracil residues.

In summary, it appears that the instant specification does not support SEQ ID NO:1905. Furthermore, GenBank Accession Number NM\_000484 and newly submitted sequence SEQ ID NO:1905 are not the same sequence since one is a DNA sequence and the other is an RNA sequence. In this regard, SEQ ID NO:1905 appears to be new matter.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 14-21, 30, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to



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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims are drawn to a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein (APP) RNA comprising SEQ ID NO:1905. It is noted that SEQ ID NO:1905 was added to the sequence listing in the Amendment filed March 10, 2007. The Examiner would like to point out that Applicants contend that SEQ ID NO:1905 represents GenBank entry NM\_000484 as disclosed at page 153 in the instant specification (see Applicant's Remarks filed March 10, 2007 at page 6, second to last paragraph). It is noted that GenBank entry NM\_000484 was submitted and made of record on the information disclosure statements filed August 7, 2006 and December 8, 2006. Comparing GenBank entry NM\_000484 with SEQ ID NO:1905 of the instant application, it is immediately noticed that the sequence of the Accession Number contains thymine residues, where SEQ ID NO:1905 has substituted the thymine residues with uracil residues.

In summary, the instant specification does not appear to support SEQ ID NO:1905. Furthermore, GenBank Accession Number NM\_000484 and newly submitted sequence SEQ ID NO:1905 are not the same sequence since one is a DNA sequence and the other is an RNA sequence. In this regard, SEQ ID NO:1905 appears to be new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 14-21, 30, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession Number NM\_000484 (submitted and made of record on Applicant's Information Disclosure Statements filed August 7, 2006 and December 8, 2006), in view of Coulson et al. (Brain Research, 1997 Vol. 770:72-80), Elbashir et al., The EMBO Journal, 2001 (submitted and made of record on Applicant's Information Disclosure Statement filed December 8, 2006), Matulic-Adamic et al. (US Patent No. 5,998,203), and/or Parrish et al., Molecular Cell, 2000 (submitted and made of record on Applicant's Information Disclosure Statement filed December 8, 2006).

Applicant is reminded that the instant application has been afforded priority to the filing date of Provisional Application 60/363,124, which is March 11, 2002. For further explanation, see the discussion above under the heading "Priority".

Claim 1 is drawn to a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein

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(APP) RNA comprising SEQ ID NO:1905, wherein about 50% to 100% of nucleotide positions in one or both strands of said siRNA molecule are chemically modified, and wherein about 50% to 100% of the purine nucleotides in one or both strands of the siNA are 2'-O-methyl purine nucleotides and about 50% to about 100% of the pyrimidine nucleotides in one or both strands of the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. Claims 3, 14-21, 30, and 35 dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein said siNA molecules comprise one or more ribonucleotides; wherein one or more purine or pyrimidine nucleotides are present on the sense strand; wherein the purine nucleotide is a 2'-deoxy purine and the pyrimidine nucleotide is a 2'-deoxy-2'-fluoro pyrimidine nucleotide; wherein the sense strand comprises a terminal cap moiety at the 5' or 3' end, or both; wherein said terminal cap moiety is an inverted deoxy abasic moiety; wherein the antisense strand comprises 2'-deoxy-2'-fluoro pyrimidine nucleotides; wherein the purine nucleotide on the antisense strand is a 2'-methyl purine nucleotide or a 2'-deoxy purine nucleotide; wherein the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense strand; wherein the 5'-end of the antisense strand includes a terminal phosphate group; and a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein (APP) RNA comprising SEQ ID NO:1905, wherein about 50% to 100% of nucleotide positions in one or both strands of said siRNA molecule are chemically modified, and wherein about 50% to 100% of the purine nucleotides in one or both strands of the siNA

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are 2'-O-methyl purine nucleotides and about 50% to about 100% of the pyrimidine nucleotides in one or both strands of the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides in a pharmaceutically acceptable carrier or diluent.

GenBank Accession Number NM\_000484 teaches the sequence of the human amyloid precursor protein (APP) gene.

Coulson et al. teach that amyloid precursor protein mediates a substrate-specific interaction between neurons and extracellular matrix components and antisense oligonucleotides targeted to the amyloid precursor protein affects adhesion of dorsal root ganglia neurons (see Abstract). Coulson et al. also teach the desire to modulate the levels and metabolism of amyloid precursor protein as a possible therapy for Alzheimer's disease (see page 78, second column).

Neither GenBank Accession Number NM\_000484 nor Coulson et al. teach a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein (APP) RNA comprising SEQ ID NO:1905, wherein about 50% to 100% of nucleotide positions in one or both strands of said siRNA molecule are chemically modified, and wherein about 50% to 100% of the purine nucleotides in one or both stands of the siNA are 2'-O-methyl purine nucleotides and about 50% to about 100 of the pyrimidine nucleotides in one or both strands of the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

Elbashir et al. teach RNA interference (RNAi) is a newly discovered pathway of inhibiting gene expression by using an antisense-like mechanism. Specifically, Elbashir

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et al. teach short interfering RNAs (siRNAs) as mediators of RNAi and inhibitors of gene expression. Detailed protocols and methods are provided for designing, preparing, testing, and using siRNA to silence/inhibit expression of virtually any known gene. Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand (see Abstract). Elbashir et al. teach modification of the internal nucleotides with 2'-deoxy or 2'-O-methyl modifications (see Abstract and Figure 4). Elbashir et al. teach that duplexes, 21 nucleotides in length, with 2 nt 3' overhangs, were the most efficient triggers of sequence-specific mRNA degradation. Elbashir et al. teach 2'-deoxythymidine in the 3' overhang (see Figures 7 and 8). Elbashir et al. teach that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function. Elbashir et al. also teach siRNA duplexes were incubated in a *D.melanogaster* RNAi/translation reaction for 15 min prior to addition of mRNAs, where the reaction mixture constitutes a pharmaceutically acceptable carrier or diluent. Elbashir et al. also teach complete substitution of one or both siRNA strands by 2'-deoxy residues and complete substitution by 2'-O-methyl residues (see page 6882, first column). It is noted that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues abolished RNAi activity, however, the instant claims do not recite any functional language, therefore, the skilled artisan would have been motivated to incorporate such substitutions/chemical modifications to a siRNA molecule as discussed below.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic

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acid structures (see Abstract). The double stranded nucleic acid RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the double stranded nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3'-phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'-deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, Cl and F are representative halogens (see column 3, for example). The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach chemically synthesized double stranded siRNA molecules comprising various modifications in the sense or antisense strand, including 2'-deoxy-2'-fluoro modifications (see Figure 5). One or both strands comprise modifications. Parrish et al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the RNA interference process (see Summary).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a chemically modified double stranded short

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interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein (APP) RNA comprising SEQ ID NO:1905 using the sequence taught by GenBank Accession Number NM\_000484, the motivation of Coulson et al., and following the methods of Elbashir et al., Matulic-Adamic et al., and Parrish et al. It would have been obvious to have about 50% to 100% of the purine nucleotides in one or both stands of the siNA be 2'-O-methyl purine nucleotides and about 50% to about 100% of the pyrimidine nucleotides in one or both strands of the siNA be 2'-deoxy-2'-fluoro pyrimidine nucleotides using the teachings and motivation of Elbashir et al. It would have been obvious to have the siNA comprised in a pharmaceutically acceptable carrier or diluent using the teachings and motivation of Elbashir et al.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to incorporate about 50% to 100% of the purine nucleotides in one or both stands of the siNA be 2'-O-methyl purine nucleotides and about 50% to about 100% of the pyrimidine nucleotides in one or both strands of the siNA be 2'-deoxy-2'-fluoro pyrimidine nucleotides to determine the tolerance of chemical modifications for RNAi activity as taught by Elbashir et al. It would have been obvious to incorporate a terminal cap moiety on one of the ends of the sense strand since Matulic-Adamic et al. taught such modifications protect the nucleic acid from exonuclease degradation. It would have been obvious to incorporate a phosphorothioate internucleotide linkage at the 3' end of the antisense strand or a terminal phosphate group at 5'-end of the antisense strand since either Elbashir et al., Matulic-Adamic et al., and/or Parrish et al. teach such

modifications protect the nucleic acid from nuclease attack.

One of ordinary skill in the art would have been motivated to make a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein (APP) RNA comprising SEQ ID NO:1905 for use as a potential therapy for Alzheimer's disease (see Coulson et al.). One would have been motivated to incorporate 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications into the chemically synthesized siRNA since these modifications were known in the art to add benefits to double stranded nucleic acids such as protection from exonuclease degradation and improve uptake of the nucleic acid (see Elbashir et al., Matulic-Adamic et al., and Parrish et al.). It was well known in the art at the time of filing to incorporate two or more modifications, including 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications, into oligonucleotides, as evidenced by Elbashir et al., Matulic-Adamic et al., and Parrish et al. Elbashir et al. demonstrated both 2'-deoxy and 2'-O-methyl modifications of double stranded oligonucleotides at the time the invention was made. Matulic-Adamic et al. taught double stranded oligonucleotides comprising more than one specific type of modification. Additionally, Parrish et al. teach various modifications to double stranded duplexes and teach that different modifications are tolerated at different locations of the duplex. Elbashir et al. and Parrish et al. demonstrate the routine nature of testing various chemical modifications for optimization and stabilization of a double stranded duplex. The cited art demonstrates that the specific modifications were extensively described in the art. One of skill in the art would be motivated to test



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modifications that are known to benefit oligonucleotide delivery and apply each of them to a double stranded nucleic acid molecule, such as siNA, or siRNA in order to optimize delivery of the nucleic acid. One of skill in the art would be motivated to incorporate chemical modifications to about 50% to 100% of the nucleotide positions in one of the strands of the nucleic acid molecule to test the overall effect on RNAi activity as taught by Elbashir et al. One of skill in the art would be motivated to have the siNA comprised in a pharmaceutically acceptable carrier or diluent to facilitate its delivery *in vitro* as taught by Elbashir et al.

There would be a reasonable expectation of success to apply each of the claimed modifications to the siNA molecules of the claimed invention because the chemistry was well known to one of ordinary skill in the art at the time the invention was made (see Elbashir et al., Parrish et al., and Matulic-Adamic et al.) and merely selecting combinations of such modifications is considered a design choice. There would be a reasonable expectation of success to apply chemical modifications to about 50% to 100% of the nucleotide positions in one or both strand(s) of the siNA molecule since Elbashir et al. taught the design of such nucleic acids was known to be successful in the art at the time the invention was made. Therefore, one would reasonably expect for such modifications to benefit the siNA as instantly claimed.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

tcg  
March 22, 2007

A handwritten signature in black ink, appearing to read "David C. Cottrell", is written over the typed name. The signature is fluid and cursive, with a large, stylized initial "D".